specification to correct the inadvertent typographical errors and to add sequence listing I.D. numbers. These corrections and additions are of a clerical nature and do not add new matter.

Claims 1-5 and 32-36 stand rejected under 35 U.S.C. § 101 as "inoperative" because applicant has not provided clinical data showing in vivo human efficacy. More particularly, the Examiner cites Harris et al., "Therapeutic Antibodies - The Coming of Age", Trends in Biotechnology, 11, pp. 42-44 (1993) for the following propositions:

> "[T]here is little future for the use of rodent monoclonal antibodies for in vivo human therapy and ... repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses." (Citations omitted.)

The Examiner also cites Waldman et al., "Monoclonal Antibodies in Diagnosis and Therapy", Science, 252, pp. 1657-62 (1991) for the following proposition:

> "[H]opes for antibody-based treatment methods engendered by in vitro and animal model studies have not correlated well with in vivo clinical trial results in patients."

The passages quoted by the Examiner do not give a fair characterization of the cited documents. Harris and Waldman do not teach that monoclonal antibodies are so unpredictable in vivo that they have no utility as human therapeutic agents. To the contrary, Waldman and Harris indicate a belief in the utility of monoclonal antibody-based therapies. For example, Harris goes on to state (p. 42):

> "However, an important conclusion, drawn from all the available data, is that chimaeric antibodies are non-toxic. This give researchers great confidence that the newer technologies generating more humanized antibodies will lead to the availability of effective therapeutics." (Emphasis added.)

Similarly, the Examiner overlooks the following statement in the opening paragraph (i.e., the abstract) of Waldman:

> "Recently, monoclonal antibody-mediated therapy has been revolutionized by advances such as ... genetic

engineering to create less immunogenic and more effective monoclonal antibodies ...."

Moreover, Waldman goes on to refer to an actual working example (p. 1657):

"[M]onoclonal antibodies that are specific for leukocyte adhesion molecules ... have been used to inhibit accumulation of neutrophils and thereby reduce tissue damage in animal models ...."

These additional passages show that the Examiner's characterization of Harris and Waldman is inconsistent with the overall thrust of either article.

Furthermore, an article immediately preceding Harris, i.e., Thorpe, "Monoclonal Antibodies: Clinical and Regulatory Issues", Trends in Biotechnology, 11, pp. 40-42 (1993) (copy enclosed), also reporting on a monoclonal antibody research meeting,* contains, in its concluding paragraph, an explicit statement on the "useful[ness]" of monoclonal antibodies:

"Overall, the consensus of the meeting was that mAbs are useful therapeutic and in vivo diagnostic agents." (Emphasis added.)

Taken together, the above passages show that the Examiner's assertion that the utility of the claimed invention would not be "believable prima facie to persons of skill in the art" is simply incorrect.

In connection with the utility rejection, the Examiner refers to MPEP § 608.01(p), which states in pertinent part:

"If the asserted utility of a compound is believable on its face to persons skilled in the art in view of the contemporary knowledge in the art, then the burden is upon the Examiner to give adequate support for lack of utility under this section."

"Proof of utility under this section may be established by clinical or in vivo or in vitro data, or combinations of these which would be convincing to those skilled in the art." (Citations omitted.)

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* "Monocloncal Antibodies: Clinical and Regulatory Issues", organized by IBC Technical Services Ltd., held in London, UK, November 17-19, 1992.

The above passages from Harris, Waldman and Thorpe, quoted by applicant, show that the clinical utility of monoclonal antibodies is, indeed, believable to persons skilled in the art. With regard to the pending claims, in particular, applicant provides in vitro data obtained using monoclonal antibodies and human cells. Therefore, persons skilled in the art would accept the utility of the claimed invention, as MPEP § 608.01(p) requires.

Applicant clearly indicates the utility of the claimed invention. For example, at page 10, lines 22-26, applicant states:

> "By preventing the interaction between the α4ß1 receptor and its ligands using antibodies or defined peptide sequences the present invention enables, for the first time, specific intervention in the migration of lymphocytes through the vascular endothelium and into tissues. The present invention, therefore has particular clinical utility in suppression of the immune response. ..."

For all of the foregoing reasons, the utility rejection should be withdrawn.

The specification stands objected to and claims 1-5 and 32-36 stand rejected under 35 U.S.C. § 112, first paragraph as "failing to provide and enabling disclosure and failing to present the best mode". There are three facets to this rejection.

First, the Examiner asserts that applicant has not disclosed "how to use α4ß1-specific antibodies therapeutically in humans". The Examiner goes on to say: "no examples have appeared in the application of α4ß1-specific immunotherapy in vivo".

In the second facet of the rejection, the Examiner asserts that applicant's two examples of antibodies that inhibit lymphocyte adhesion in vitro do not support claims to the use of any α4ß1-specific antibody to inhibit lymphocyte adhesion.

The rejection is not warranted on the basis of either of the Examiner's first two arguments. There exists an extensive technology for the therapeutic use of monoclonal antibodies in humans. One of ordinary skill in the art would be well aware of that technology, which is applicable in the practice of the present invention. An application is not to be read in a vacuum.

> "'Patents are ... written to enable those skilled in the art to practice the invention.' A patent need not disclose what is well known in the art." In re Wands, 858 F.2d 731, 735, 8 USPQ2d 1400, 1402 (Fed.Cir. 1988) (citations omitted).

Moreover, even if one assumes for the sake of argument that one of skill in the art were not already aware of the technology for using monoclonal antibodies therapeutically, the application is still enabling. In the specification (page 17, line 17 to page 18, line 18), applicant provides guidance regarding "antibodies for therapeutic use" by way of general discussion and five specific references.* Such guidance, taken in context of ordinary skill in the art, is sufficient to satisfy enablement requirements.

In the third facet of the rejection, the Examiner asserts that the specification does not provide a repeatable method for obtaining monoclonal antibodies P4C2, P4C10, P4G9 and P3E3 and states that they do not appear to be publicly available. The Examiner states, however, that deposit of the

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* Teng et al., "Construction and Testing of Mouse-Human Heteromyelomas for Human Monoclonal Antibody Production", Proc. Natl. Acad. Sci. USA, 80, pp. 7308-12 (1983); Kozbor et al., "The Production of Monoclonal Antibodies from Human Lymphocytes", Immunol. Today, 4, pp. 72-79 (1983); Olsson et al., "Human-Human Monoclonal Antibody-Producing Hybridomas: Technical Aspects", Meth. Enzymol., 92, pp. 3-16 (1983). Morrison et al., "Chimeric Human Antibody Molecules: Mouse Antigen-Binding Domains with Human Constant Region Domains", Proc. Natl. Acad. Sci. USA, 81, pp. 6851-55 (1984); and Takeda et al., "Construction of Chimaeric Processed Immunoglobulin Genes Containing Mouse Variable and Human Constant Region Sequences", Nature, 314, pp. 452-54 (1985).

hybridomas that produce monoclonal antibodies P4C2, P4C10, P4G9 and P3E3 would overcome this facet of the rejection.

Applicant does not understand why the Examiner states that deposit-identifying information should be added to the specification pursuant to 37 C.F.R. § 1.809(d). The required deposit information is already present in the specification, as filed, at page 74, lines 14-22.

As shown by the Declaration Of Assignee* (submitted herewith) and the attached copy of the ATCC Receipt In The Case Of An Original Deposit (submitted herewith), hybridomas that produce monoclonal antibodies P3E3, P4G9, P4C10 and P4C2 (assigned ATCC accession numbers HB10212, HB10213, HB10214, and HB10215, respectively) were deposited at the American Type Culture Collection, under the terms of the Budapest Treaty, on September 1, 1989. The Declaration states that all restrictions imposed by the depositor on the availability to the public of the deposited materials will be irrevocably removed upon the granting of a patent. This overcomes the third facet of the above-described non-enablement rejection.

Claims 1-5 and 32-36 stand rejected further under 35 U.S.C. § 112, first and second paragraphs. The Examiner asserts that the recitation of "a fragment or derivative thereof" renders the claims "indefinite". The Examiner suggests that "antigen-binding fragments" would be "a clearer term".

In accordance with the Examiner's suggestion, applicant has amended claims 1 and 32 to recite "antigen binding region" instead of "fragment or derivative". This overcomes the rejection (claims 2-5 depend directly or indirectly from claim 1; claims 33-36 depend directly or indirectly from claim 32).

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* Executed on behalf of Fred Hutchinson Cancer Research Center by Catherine J. Hennings, Manager, Technology Transfer.

Support for this amendment is found in the specification at page 17, lines 27-30. Therefore, this amendment does not constitute new matter.

Claim 32 stands rejected under 35 U.S.C. § 112, first and second paragraphs. The Examiner asserts that because the characteristics of an "extracellular matrix receptor", recited in claim 32, are unknown, the use of that terminology renders the claim "indefinite". The Examiner suggests amendment of claim 32 so that it incorporates the "α4ß1 receptor" limitation found in claim 33.

Applicant has amended claim 32 to recite "α4ß1 receptor", as suggested by the Examiner. This overcomes the rejection. Since this amendment merely moves a limitation up from claim 33 to claim 32, it does not add new matter. Applicant has cancelled claim 33 as duplicative of amended claim 32.

Claims 1-4 and 32-35 stand rejected under 35 U.S.C. § 103 as obvious over Shimizu et al. ("Roles of Adhesion Molecules in T-Cell Recognition: Fundamental Similarities between Four Integrins on Resting Human T Cells (LFA-1, VLA-4, VLA-5, VLA-6) in Expression, Binding, and Costimulation", Immunol. Rev., 114, pp.109-43 (1990)) in view of Carlos et al. ("Membrane Proteins Involved in Phagocyte Adherence to Endothelium", Immunol. Rev., 114, pp. 5-25 (1990)) and Wayner et al. ("Identification and Characterization of the T Lymphocyte Adhesion Receptor for an Alternative Cell Attachment Domain (CS-1) in Plasma Fibronectin", J. Cell Biol., 109, pp. 1321-30 (1989)).

By virtue of the above amendment to the specification, fulfilling the requirements for priority, applicant is entitled to an effective filing date of September 1, 1989. The subject

matter of claims 1-4 and 32-36 is fully supported by the September 1, 1989 disclosure filed in the parent application.

The publication dates of Shimizu, Carlos and Wayner are 1990, 1990 and September 1, 1989,* respectively. Since none of these references was published before applicant's effective filing date, they are not prior art to the present application. Therefore, the obviousness rejection over Shimizu, Carlos and Wayner should be withdrawn.

Claims 5 and 36 stand rejected under 35 U.S.C. § 103 as obvious over Shimizu, Carlos and Wayner (as described above for claims 1-4 and 32-36), and further in view of Carter et al. ("The Role of Integrins α2ß1 and α3ß1 in Cell-Cell and Cell-Substrate Adhesion of Human Epidermal Cells", J. Cell Biol., 110, pp. 1387-1403 (1990)).

As discussed above, applicant is entitled to an effective filing date of September 1, 1989. Carter was published in April 1990. Since neither Shimizu, Carlos, Wayner nor Carter was published before applicant's effective filing date, none of those references constitutes prior art with respect to the present application. Therefore, the obviousness rejection over Shimizu, Carlos, Wayner and Carter should be withdrawn.

Claims 1-4 and 32-35 stand rejected under 35 U.S.C. § 103 as obvious over Hemler, "Adhesive Protein Receptors on Hematopoietic Cells", Immunol. Today, 9, pp. 109-113 (1988); Stoolman, "Adhesion Molecules Controlling Lymphocyte Migration", Cell, 56, pp. 907-910 (1989), and Pitzalis et al., "The Preferential Accumulation of Helper-Inducer T Lymphocytes in Inflammatory Lesions: Evidence for Regulation by Selective

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* Applicant has enclosed herewith a letter from Jennifer Callahan, of Rockefeller University Press, establishing that September 1, 1989 was the official mailing date for the September 1989 issue of the Journal of Cell Biology.

Endothelial and Homotypic Adhesion", Eur. J. Immunol., 18, pp. 1397-1404 (1988). The Examiner asserts that Hemler teaches "that VLA4 composed of α4ß1 is expressed on nearly all lymphocytes, monocytes and related cell lines". The Examiner further asserts that Hemler also teaches "the importance of adhesion molecules for leukocyte adherence to vascular endothelium cells". The Examiner asserts that Stoolman teaches that a monoclonal antibody designated LPAM-1 "effectively blocked lymphoid-endothelial cell binding and that this antibody specifically cross-reacted with anti-human VLA-4". The Examiner further asserts that Stoolman teaches "that blocking lymphocyte-endothelial interactions could be accomplished by anti-adhesion antibodies". The Examiner asserts that Pitzalis teaches that high levels of CD29, which contains the VLA ß1 subunit, are "characteristic of" lymphocytes at sites of inflammation.

The Examiner puts all of the foregoing assertions together to arrive at the following conclusion:

> "[I]t was known at the time the invention was made that α4ß1 and ß chain-expressing cells were involved at inflammatory sites and that anti-adhesion antibody treatment inhibited leukocyte-endothelial cell interactions in vitro and in vivo ... From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention."

As explained below, the Examiner's conclusion that applicant's invention was obvious does not reasonably follow from a clear understanding of the contents of the cited documents.

In asserting that Hemler teaches the importance of adhesion molecules for leukocyte adherence to vascular endothelium cells preceding leukocyte emigration, the Examiner fails to recognize that the Hemler statement in question refers specifically to "the leukocyte receptors LFA-1, Mac-1 and/or p150,95 (citations omitted)" -- not to VLA-4, which is discussed

elsewhere in the Hemler reference. At the time that Hemler was written, the function of VLA-4 was unknown.

The monoclonal antibody LPAM-1 results referred to by Stoolman, a review article, were obtained and published by Holzmann et al. ("Identification of a Murine Peyer's Patch-Specific Lymphocyte Homing Receptor as an Integrin Molecule with an α Chain Homologous to Human VLA-4α", Cell, 56, pp. 37-46 (1989)). In several critical respects, the present invention is distinguished over the Holzmann results mentioned in Stoolman.

The Holzmann results were obtained using high endothelial venules ("HEVs"). HEVs comprise a specialized form of endothelial cells involved in the lymphocyte recirculation pathway. Moreover, monoclonal antibody LPAM-1 only inhibited binding of lymphoid cells to Peyer's patch HEVs -- not peripheral node HEVs. Peyer's patch HEV are a specialized form of HEV found only in the gut. Thus, the LPAM-1-mediated inhibition was reported for only a specialized subset of a specialized subset of endothelial cells.

More importantly, the cells referred to by Holzmann were in a normal, resting, i.e., non-activated state. In contrast, the present invention involves inhibition of lymphocyte binding to inflammatory cytokine-activated endothelial cells. It is well-known that activation of endothelial cells induces surface expression of endothelial cell-leukocyte adhesion molecules such as ICAM-1, ELAM-1 and VCAM-1. This means that activated endothelial cells have leukocyte binding capacities not present in non-activated endothelial cells. It follows that the ability to inhibit binding of leukocytes to non-activated endothelial cells may not correlate with the ability to inhibit binding of leukocytes to activated endothelial cells. For this reason, if no other, the

Holzmann data referred to by Stoolman fail to suggest the present invention.

Finally, there is the fact that the Holzmann data in Stoolman are murine data. The present invention is directed to inhibiting human leukocyte-endothelial cell adhesion. Thus, in the cited reference, the cell type is different, the experimental treatment is different, and the species from which the cell comes is different.

The Examiner's emphasis on Pitzalis referring to a preponderance of CDw29-expressing T-cells at inflammatory lesions is reflects hindsight and oversimplification. Although CDw29 shares the ß1 subunit in common with VLA4 (α4ß1), the ß1 subunit associates with at least six different subunits, all of which can be found on T-cells. The information in Pitzalis, does not indicate or suggest that applicant's monoclonal antibodies would have the advantageous properties demonstrated by the present invention.

The scattered pieces of information that the Examiner points to in Hemler, Stoolman and Pitzalis, are, at best, consistent with applicant's discovery in the present invention. By any reasonable reading, however, they do not predict applicant's invention or render the invention obvious. The Examiner combines those references only with the benefit of hindsight, which is not permissible. Furthermore, even if one assumes for the sake of argument that there were a suggestion to combine those three references, they do not teach or suggest applicant's invention -- even in combination. Therefore, the obviousness rejection over Hemler, Stoolman and Pitzalis should be withdrawn.

Applicant submits the following Supplemental Statement under 37 C.F.R. §§ 1.56 and 1.97. Applicant, through its

attorney or agent, makes of record the following document (copy enclosed):*

Dufour et al., "Attachment, Spreading and Locomotion of Avian Neural Crest Cells are Mediated by Multiple Adhesion Sites on Fibronectin Molecules", EMBO J., Vol. 7, pp. 2661-71 (1988).

Applicant respectfully requests: (1) that the Examiner fully consider this document during examination of this application; (2) that the "Notice of References Cited" issued in this application list this document; and (3) that a list including this document be printed on any patent issuing from this application.

The above-cited document, made of record by applicant herein, neither alone nor in combination with any other document, renders unpatentable any pending claim in this application.

Because the present application was filed more than three months ago and a first Office Action has been mailed, applicant encloses a check in the amount of $200.00, as required under 37 C.F.R. §§ 1.17(p) and 1.97(c). The Commissioner is hereby authorized to charge payment of any additional fees, or credit any overpayment, to Deposit Account No. 06-1075.

Applicant filed a Second and a Third Supplemental Information Disclosure Statement in this application on April 14, 1993 and June 9, 1993, respectively. Applicant requests that the Examiner include, with the next Office Action, initialed copies of the document-listing forms submitted with those Supplemental Information Disclosure Statements.

Enclosed for return to the Examiner are three documents received, apparently by mistake, with the June 15, 1993 Office Action (Paper No. 16):

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* For the convenience of the Examiner, a completed Form PTO-1449 is attached.

(1) a duplicate copy of the Stoolman article;

(2) the Patent and Trademark Office's copy of the Form PTO-892 listing the Pitzalis article; and

(3) an article by Laurelee Osborn ("Leukocyte Adhesion to Endothelium in Inflammation", Cell, 62, pp. 3-6 (1990)), which is not discussed in the June 15, 1993 Office Action.

Appliant assumes that the enclosure of these documents with the Office Action was inadvertent.

An Associate Power of Attorney for the undersigned is enclosed herewith.

Applicant respectfully requests that the Examiner reconsider the application in light of the foregoing amendments and remarks, and allow the claims of this application. Should the Examiner believe that a conference with applicant's attorney or agent would be helpful, he is invited to telephone the undersigned at any time at (212) 596-9000.

Respectfully submitted,

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I Hereby Certify that this Correspondence is being Deposited with the U. S. Postal Service as First Class Mail in an Envelope Addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on December 7, 1993

Thomas Quinones
Name of Person Signing

Thomas Quinones
Signature of Person Signing